REMARKS

A. Status of the Claims

Currently, claims 40-85, 87-90, 139 and 140 are under examination. Claims 42-85 are withdrawn from consideration. Claims 40, 41, 87-90, 139 and 140 stand rejected.

Claims 40, 41, 139 and 140 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over international application number WO 96/11712 to Kayyem et al. ("Kayyem"), in view of U.S. Patent No. 7,008,924 to Yan et al. ("Yan") and U.S. Patent No. 5,989,545 to Foster et al. ("Foster").

Claims 40, 41, 87-90, 139 and 140 are provisionally rejected on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1, 10-24, 30, 31, 33-50, 57 and 59-61 of co-pending Application No. 10/591,486 ("the '486 application").

Claims 40, 41, 87-90, 139, and 140 are provisionally rejected on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1, 10-24, 30, 31, 33-50, 57, 59-61, and 63-66 of co-pending Application No. 11/073,307 ("the '307 Application").

B. Explanation of the Amendments

In this paper, Applicants have amended claim 40 to correct a minor punctuation error and to improve the readability by adding the word "and". No new matter has been added by these amendments.

C. Election of Species

Further to the telephone conversation between Examiner and Applicants' representative on May 8, 2008, Applicants confirm the election of "botulinum toxin" as the

species for prosecution, which is readable on claims 40, 41, 87-90, 139, and 140. Applicants also confirm that this election is made without traverse.

D. Applicants' Claims Are Patentable Over Kayyem in view of Yan and Foster

Applicants respectfully traverse the rejection of claims 40, 41, 139 and 140 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Kayyem, in view of Yan and Foster. The traversal is based on at least the following grounds: (1) the combination of references fails to teach or suggest all of the features of the claimed invention; (2) Kayyem itself teaches away from the claimed invention; and (3) the Office Action's proposed combination of references impermissibly changes the principle of operation of Yan and Kayyem. For at least these reasons, the rejection under 35 U.S.C. § 103(a) should be withdrawn.

1. The Combination of References Fails to Teach or Suggest All of the Features of the Claimed Invention

In formulating the rejection under 35 U.S.C. § 103(a), the Office Action attempts to combine various aspects of Kayyem, Yan and Foster to arrive at Applicants' invention. However, the Office Action's proposed combination of references is deficient, because it fails to teach or suggest all of the features of Applicants' claimed invention. For example, the proposed combination of references fails to teach or suggest all of the elements of independent claim 40, which reads as follows:

> 40. A composition comprising a non-covalent association complex of:
>
> a positively charged backbone covalently attached to a plurality of amino acid sequences, wherein said amino acid sequences are selected from the group consisting of

> $(gly)_p$-RGRDDRRQRRR-$(gly)_q$ (SEQ ID NO:19), and $(gly)_p$-YGRKKRRQRRR-$(gly)_q$ (SEQ ID NO: 20) wherein p and q are each independently an integer of from 0 to 20;
>
> a negatively charged backbone having a plurality of attached targeting agents;
>
> a negatively charged backbone having a plurality of attached biological agents, wherein each of said biological agents is a therapeutic agent or a cosmeceutical agent and not a nucleic acid;
>
> wherein said non-covalent association complex carries a net positive charge.

Notably, the non-covalent association complex recited in claim 40 comprises three components: (1) "a positively charged backbone covalently attached to a plurality of amino acid sequences…"; (2) "a negatively charged backbone having a plurality of attached targeting agents"; and (3) "a negatively charged backbone having a plurality of attached biological agents." Furthermore, claim 40 specifies that the non-covalent association complex carries a "net positive charge."

The Office Action's proposed combination of references does not teach or suggest all of these claimed features. For example, the proposed combination of references fails to teach or suggest a "non-covalent association complex" that "carries a net positive charge." Nowhere does the proposed combination of references teach or suggest this feature of the claimed invention. To the contrary, Kayyem states that "[g]enerally, after complex formation, the polycomplexes are approximately electrically neutral, since electroneutrality is generally necessary to achieve high transfection efficiency." [Kayyem, p. 10, lines 4-6]. Towards this goal, Kayyem provides methods for achieving electroneutrality, stating "the length and extent of derivatization of the polymers with cell targeting moieties and physiological agents may be varied to achieve electroneutrality" [Kayyem, p. 10, lines 6-7].

Furthermore, the mere possibility that Kayyem's complexes might carry a positive charge and therefore not be exactly electroneutral is insufficient, as a matter of law, to establish that some embodiments of Kayyem's complexes might be inherently positively charged. As noted by the Court of Appeals for the Federal Circuit, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added).

Neither Yan nor Foster alleviates this deficiency of Kayyem, as neither reference teaches or suggests a "non-covalent association complex" that "carries a net positive charge", as recited in independent claim 40.

Therefore, because the combination of references fails to teach or suggest all of the features of the claimed invention, the rejection under 35 U.S.C. § 103(a) should be withdrawn. See In re Royka, 490 F.2d 981, 985 (CCPA 1974) (stating that obviousness requires a suggestion of all limitations in a claim).

2. Kayyem Teaches Away from the Claimed Invention

As noted in the foregoing section, the specification of Kayyem requires its polycomplexes to possess "significant electroneutrality" [Kayyem p. 21, lines 12-14]. In direct contrast, Applicants' pending claims specify that the claimed "non-covalent association complexes" carry "a net positive charge." As an electroneutral substance does not, by definition, carry a positive charge, Kayyem teaches away from the claimed invention.

3. The Proposed Combination of References Improperly Changes in the Principle of Operation of Yan

In its attempt to combine Kayyem, Yan and Foster to arrive at the claimed invention, the Office Action asserts that "[o]ne would have been motivated to attach the peptide [of Yan] to the cationic polymer [of Kayyem] because the peptide is strongly cationic, and the invention of Kayyem depends on the interaction of oppositely charged polymers to form a complex." [Office Action, p. 6]. The Office Action further contends that "one of ordinary skill in the art when deciding which polymer to attach the peptide to, would opt to place it on the like-charged cationic polymer in order to avoid interfering with the charge interaction between the cationic and anionic polymers" [Office Action, p. 6].

Applicants take issue with this proposed combination of Kayyem and Yan, because it impermissibly changes the principle of Yan. See In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (stating that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.) Yan reports the use of the HIV-TAT fragment YGRKKRRQRRR for transport, but only in the context of directly attaching the fragment by a covalent bond to the therapeutic or imaging agent that is to be delivered into the cell. For example, Yan reports fluoroscein isothiocyanate (FITC) constructs and β-galactosidase fusion proteins wherein FITC and β-galactosidase are covalently conjugated to an amino acid comprising the sequence YGRKKRRQRRR. [Yan, col. 35, lines 30-40]. With respect to polypeptides, Yan states that "[i]t will thus be appreciated that the tat protein sequence may be used to internalize a desired polypeptide into a cell." [Yan, col. 35, lines 44-45].

The Office Action proposes to attach the amino acid sequence YGRKKRRQRRR to Kayyem's polymeric molecule, rather than to the targeting, therapeutic, or contrast agents reported by Kayyem. However, Kayyem's polymeric molecule is not acknowledged by Kayyem to possess any benefits with respect to targeting, therapeutic treatments, or imaging. As such, the Office Action's proposed modification of Kayyem's polymeric molecule is inconsistent with Yan, because a faithful reading of Yan would suggest directly attaching the amino acid sequence YGRKKRRQRRR to the targeting, therapeutic, or contrast agents reported by Kayyem, and not to Kayyem's polymeric molecule. In this way, the Office Action's proposed modification of Kayyem improperly changes the principle of operation of Yan, because Yan's method of transport involves directly attaching the amino acid sequence YGRKKRRQRRR to the therapeutic or imaging agent of interest.

Furthermore, Applicants also strongly disagree with the Office Action's statement that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to attach a peptide of SEQ ID NO: 20 [i.e., $(gly)_p$-YGRKKRRQRRR-$(gly)_q$] to the cationic polymer of Kayyem in order to facilitate cellular uptake of the complex" (emphasis added). Indeed, to Applicants' knowledge, there is no teaching in the art, prior to Applicants' disclosure, that attachment of efficiency groups (e.g., SEQ ID NO. 20) to a positively charged backbone would increase the transport of a non-covalent complex containing such a positively charged backbone.

Indeed, one of the inventive concepts disclosed by Applicants is that the use of such a positively charged backbone in a non-covalent complex leads to significantly enhanced transport of active agents that are non-covalently associated with the positively charged backbone. For example, in Example 3 of the original specification, Applicants report a

comparative study that included the following two types of non-covalent complexes: (1) a plasmid expressing blue fluorescent protein driven, non-covalently complexed to polylysine (150,000 D) (Mixture 1); and (2) a plasmid expressing blue fluorescent protein, non-covalently complexed to polylysine (150,000 D) with attached to -Gly_3Arg_7 efficiency groups (Mixture 4). These two types of non-covalent complexes were added to cell cultures containing primary human aortic smooth muscle cells. Subsequent spectrophotometric analysis showed statistically significant enhancement of gene delivery for the non-covalent complexes containing polylysine with attached -Gly_3Arg_7 efficiency groups, as compared to complexes containing polylysine without the attached efficiency groups [see original specification, pp. 24-25]. Thus, Applicants have disclosed that positively charged backbones with attached efficiency groups promote transport of the non-covalently associated complexes.

In contrast, the Office Action does not provide any basis for its statement that one of ordinary skill in the art would find it obvious to modify the cationic polymer of Kayyem using the amino acid sequence recited in Yan in order to facilitate cellular uptake of the complex. None of the cited references teach or suggest such a concept, and the Office Action's proffered motivation to combine Kayyem and Yan "in order to facilitate cellular uptake of the complex" appears to be no more than impermissible hindsight reasoning based on Applicants' own disclosure.

To summarize, the Office Action's proposed combination of references improperly changes the principle of operation of Yan. Further, the Office Action's proffered motivation to combine Kayyem and Yan "to facilitate cellular uptake of the complex" is unsubstantiated by any objective evidence and is based on impermissible hindsight reasoning.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

D. Double Patent Rejections

The Examiner has provisionally rejected claims 40, 41, 87-90, 139 and 149 as allegedly being the same invention as the invention recited in claims 1, 10-24, 30, 31, 33-50, 57, and 59-61 of co-pending application no. 10/591,486. Further, claims 40, 41, 87-90, 139, and 140 are provisionally rejected as allegedly being the same invention as the invention recited in claims 1, 10-24, 30, 31, 33-50, 57, 59-61, and 63-66 of co-pending application no. 11/073,307.

Applicants respectfully request that this provisional rejection be held in abeyance until the other rejections in this case are overcome and the claims of this case are otherwise in condition for allowance. Applicants reserve the right to file a terminal disclaimer in the event that it is deemed necessary in a later stage of prosecution.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13720-105065US1.

Respectfully submitted,
KING & SPALDING, L.L.P.

Dated: November 17, 2008

By: /Joseph D. Eng Jr./
Joseph D. Eng Jr.
Registration No. 54,084

Correspondence Address:
KING & SPALDING, L.L.P.
1185 Avenue of the Americas
New York, NY, 10036-4003
(212) 556 - 2100 Telephone
(212) 556 - 2222 Facsimile